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TITLE: Genetic and Environmental Influences on the Pathogenesis of Parkinson's Disease: Young Adult Brain and Behavioral Risk Indicators

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CONTRACTING ORGANIZATION: Columbia University, New York, NY

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14. ABSTRACT

This study addresses questions about the causes and progression of Parkinson's disease (PD) over the life course, specifically with respect to the role of a toxic chemical exposure, chlorpyrifos (CPF), an organophosphate pesticide. To understand how early exposure to CPF affects the nervous system, genetic susceptibility to CPF, and the long-term consequences of exposure, we are studying 200 young adults in an urban community cohort, now reaching 19-20 years of age, many of whom were routinely exposed to residential pesticides, as measured by a biomarker of CPF in cord blood. We are conducting neurological assessments of stiffness and gait, cardiac measures, sleep questions, measures of tremor, olfactory status, and other neuropsychological measures. We have access to previously-collected genetic information. The assessment requires 45-50 minutes; participants are paid $100 and cost of transportation. The purpose is to identify the earliest signs of risk for later PD that may appear long before clinical and motor symptoms can be seen, and to determine who is at greatest risk. We hypothesize that the individuals who were most highly exposed to CPF during the prenatal period (based on cord blood sample) will be more likely to show pre-motor and pre-clinical symptoms on these tests, as compared to individuals with lower exposure, and that some individuals may be more susceptible to exposure based on their genetic characteristics.

15. SUBJECT TERMS
None listed.

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1. Introduction

This study addresses the role of toxic chemical exposures, organophosphate pesticides (OPs), that may contribute to our understanding of the causes and progression of Parkinson's disease over the life course. To date, there is little knowledge about how OPs inflict nerve damage potentially resulting in parkinsonian symptoms, and even less information about how early in life the non-motor and pre-clinical signs of damage can be seen. To learn more about how these chemicals attack the nervous system, genetic susceptibility to these chemicals, and the long-term consequences of exposure, we will study an urban minority birth cohort, now reaching 19-20 years of age, many of whom were routinely exposed to residential OP use, prior to the indoor residential ban in 2001. We invite 200 of these young adults to participate in an examination, including neurological measures of stiffness and gait, cardiac measures, sleep questions, measures of tremor, and other neuropsychological measures. We also have access to genetic information, previously collected on the individuals. The assessment requires 45-50 minutes, and the purpose is to identify the earliest signs of risk for later PD that may appear long before clinical and motor symptoms can be seen. We hypothesize that the individuals who were most highly exposed during the prenatal period (based on a cord blood sample) will be more likely to show pre-motor and pre-clinical symptoms, as compared to individuals with lower exposure, and that some individuals may be more susceptible to the exposure based on their genetic characteristics.

2. Keywords

Parkinson's disease
Parkinsonism
Neurodegenerative disease
Neurotoxicity
Environmental exposure
Pesticides

3. Accomplishments

3a. Major Goals

Goal 1: Identify signs of early PD risk in the form of neurological dysfunction, REM sleep behavior disorder, autonomic dysfunction, and olfactory deficits in a sample of 200 19-20 year old individuals selected from a prospective cohort with varying levels of prenatal CPF exposure, as previously measured

Milestones associated with Goal 1:

- Number of assessments to be counted as completed to achieve an average rate of 1-2 assessments/week
- Neurological examinations completed in face-to-face assessment (85% completion)
- Behavioral, olfactory and survey measures completed (85% completion)
- The Actiheart reads, meetings, processing and supervision will follow the same schedule (85% completion)
- Data entry and programming will begin in the 3rd month, after a lag time for the setting up of data entry screens, and will continue through the 30th month (85% completion)
- The review of the clinical assessments will be conducted as the examinations are completed (85% completion)

Goal 2: Measure associations between prenatal CPF concentrations (previously collected data) and signs of early PD risk (as identified in Goal 1)

Milestones associated with Goal 2 (statistical analyses have commenced, although data collection is ongoing, and will now be conducted through the 40th month of the project, including the period of the no cost extension):

- Statistical analysis of associations between prenatal CPF and tremor measure (a neurological assessment) (50% completion)
- Statistical analysis of associations between prenatal CPF, neurological measures, REM sleep behavior disorder, autonomic dysfunction (Actiheart), cognition and olfactory deficits (20% completion)
- Preparation of papers and reports (0% completion)

Goal 3: Stratify the sample and measure associations between selected *PON1* gene variants and signs of early PD risk, regardless of exposure

Milestones associated with Goal 3 (no statistical analyses have commenced, since data collection is ongoing, and will now be conducted through the 40th month of the project, including the no cost extension):

- Characterization of *PON1* genotype distribution (85% completion)
- Statistical analysis of main associations between *PON1* gene variants and all indicators of early PD risk (neurological measures, REM sleep behavior disorder, autonomic dysfunction--Actiheart, cognition and olfactory deficits) (0% completion)
- Preparation of papers and reports (0% completion)

Goal 4: Test for effect modification of the primary CPF exposure-PD risk outcome by subject genotype; conduct exploratory analyses of this effect modification using various combinations of maternal and child *PON1* gene variants to potentially identify those subjects who would be expected to be most susceptible to the adverse impact of CPF exposure on PD risk symptoms

Milestones associated with Goal 4 (no statistical analyses have commenced, since data collection is ongoing, and will now be conducted through the 40th month of the project, including the no cost extension):

- Exploratory statistical analysis of the interaction effect of CPF and genotype (*PON 108* and *PON 192*) on neurological symptoms, physiological measures, and behaviors (0% completion)
- Preparation of papers and reports (0% completion)

3b. Activities, Objectives and Results to Date

Goal 1: Identify signs of early PD risk in the form of neurological dysfunction, behavioral and cognitive anomalies, REM sleep behavior disorder, autonomic dysfunction, and olfactory deficits in a sample of 200 19-20 year old individuals selected from a prospective cohort with varying levels of prenatal CPF exposure, as previously measured

Specific Objectives:

- Conduct a 45-60 minute assessment on each recruited and consented individual
- Neurological/clinical components of the assessment to include evaluations of extrapyramidal motor dysfunction, dystonia, bradykinesia and tremor
- Behavioral and physiological components to include evaluations of non-motor symptoms, REM sleep behavior disorder, cognitive components, and autonomic dysfunction (heart rate variability), and olfactory deficits

Major Activities:

A. *Implementation of the Protocol*

The following tools/methods, comprising the neurological, behavioral and physiological protocol continued to be implemented during this 6-month project period:

- D-KEFS (Delis-Kaplan Executive Function System) Trail Making Test: 5 conditions
- D-KEFS Color-Word Interference Test (Stroop Test)
- CANTAB (Cambridge Neuropsychological Test Automated Battery [CANTAB] includes highly sensitive, precise and objective measures of cognitive function, correlated to neural networks. We measure: Episodic memory, Working memory, Executive function, Planning, Information processing. The specific tests include: Motor Screening Task (MOT), Paired Associates Learning (PAL), Reaction Time (RTI), Pattern Recognition Memory (PRM), One Touch Stockings of Cambridge (OTS), and Spatial Working Memory (SWM)
- Timeline Followback (TLFB) (Sobell and Sobell, 1992; Del Boca and Darkes, 2003) is one of several self-report tasks used to measure alcohol consumption, and is characterized by a retrospective daily self-report of alcohol use quantity for a period of time (often 30 days) preceding the assessment day. Also included is a 30 day recall use for Nicotine, Cannabis and other drugs
- BAI: Beck Anxiety Inventory® (BAI®) is a brief, criteria-referenced assessment for measuring anxiety severity and level
- BDI: Beck Depression Inventory®-II (BDI®-II) is a brief, criteria-referenced assessment for measuring depression severity
- COMPASS 31: This brief interview asks questions about movement, constipation, eye and mouth symptoms, and other autonomic functions.
- RBDSQ: REM sleep Behavior Disorder Screening Questionnaire to facilitate the identification of subjects with REM Sleep Behavior Disorder.
- UPDRS: Unified Parkinson's Disease Rating Scale
- Fahn-Marsden Scale (F-M) measures dystonia
- Spiral: ten Archimedean spirals with each hand inside a 10x10 cm square on 8.5x11 inch letter-size paper, using a wireless, inked writing pen on a 9x12 inch digitizing graphics tablet (Intuos 4,Wacom technology, Vancouver, WA) connected via standard USB to a computer using proprietary software.
- UPSIT: The University of Pennsylvania Smell Identification Test
- Actiheart (Heart Rate Variability device and software)

B. *Quality Control and Safety Read*

Dr. Sloan regularly reviews all HRV data. Any child scoring in the abnormal range on any measure has been contacted directly, and permission obtained to contact his/her physician for potential referral to the New York Presbyterian Hospital for clinical evaluation to confirm diagnosis of any serious disorder and to offer treatment if needed.

C. *Reimbursement for Travel and Volunteer Payment*

This was accomplished according to university policies involving a secure system to distribute and monitor cash payments at the time of the assessment.

D. *Institutional Review Board Approval*

Ongoing.

E. *Recruitment, Informed Consent, Scheduling and Testing*

Beginning with the oldest individuals in the eligible cohort, we have enrolled and tested 140 subjects. The full study team has met regularly to coordinate and monitor all start-up activities throughout the study period.

Results:

- Data Collection: N=176 subjects have been assessed to date, 26 of whom received remote visits only (during COVID pause) and are being scheduled to return for the clinical assessments.
- Data entry: All data that have been collected (described above) have been entered into the master data system. David Merle continues to oversee the data cleaning, entry and storage.
- Review of genetic data: in process.

Goal 2: Measure associations between prenatal CPF concentrations (previously collected data) and signs of early PD risk, as identified in Goal 1

Major activities and objectives:

Statistical analyses that integrate clinical, behavioral and physiological data await the completion of data collection and data entry. During this project period, we began the bivariate and adjusted analysis of the spiral data.

Results:

- Preliminary data analyses have been conducted using the spiral/tremor data as the dependent variable. Moderate signal is present in spiral width variability and second order smoothness in the non-dominant hand. Specifically, the difference between the subject's drawing curve and the linear curve of best fit gives an estimation of the spatial error that the subject made when drawing the spiral, called the first order smoothness. The second order zero crossing describes the amount and rate at which the unraveled spiral crosses the line of best fit. This suggests that the highly exposed subjects display less smoothness when drawing the spiral with their non-dominant hand, and the drawings have more variability between spirals as compared to subjects with low exposure.
- Preliminary bivariate data analyses have been conducted on the measure of gait, suggesting that the highly exposed subjects exhibit a significant gait anomaly, as compared with low exposed subjects. We are in the process of interpreting this finding.

Goal 3: Stratify the sample and measure associations between selected *PON1* gene variants and signs of early PD risk, regardless of exposure

Major activities and objectives:

Statistical analyses awaiting the completion of data collection are as follows: (a) analyze the distribution of polymorphisms and the associations between genetic factors and chlorpyrifos blood levels in mother and infan; (b) test the main associations between CPF exposure, genotype and known level of enzyme activity; and (c) explore the interaction effect of CPF and genotype (*PON108* and *PON192*) on neurological symptoms, physiological measures, and behaviors.

Results:

Nothing to report

Goal 4: Test for effect modification of the primary CPF exposure-PD risk outcome by subject genotype; conduct exploratory analyses of this effect modification using various combinations of maternal and child *PON1* gene variants to potentially identify those subjects who would be expected to be most susceptible to the adverse impact of CPF exposure on PD risk symptoms

Major activities and objectives:

Statistical analyses to accomplish this objective await the completion of data collection and data entry.

Results:
Nothing to report

3c. Opportunities for training and professional development

Nothing to report

3d. Dissemination of results to communities of interest

Nothing to report

3e. Plans for the next reporting period to accomplish goals

We plan to continue to work on Goals 1-4 during the no coat extension period. We do not anticipate any changes in objectives and scope. We plan to recruit and assess approximately 30 additional subjects from the parent cohort. With respect to Goal 1, we will continue to recruit subjects from the parent cohort, with varying levels of prenatal CPF exposure, for the purpose of assessing current neurological and neuropsychological function. The aim is to assess the prevalence of pre-clinical extrapyramidal motor dysfunction (dystonia, bradykinesia, arm tremor), prevalence of non-motor symptoms (REM sleep behavior disorder, autonomic dysfunction, cognitive anomalies, and olfactory deficits), which are known to precede motor symptoms in PD; and to subsequently link early CPF exposure to these outcomes. In addition, we will continue data cleaning and entry with the Data Coordinating Center (DCC) where all data will be deposited and integrated with previously-collected cohort data, some variables of which are used as covariates in the analyses.

4. Impact

4a. Impact on the development of the principal discipline(s)

Nothing to report

4b. Impact on other disciplines

Nothing to report

4c. Impact on technology transfer

Nothing to report

4d. Impact on society beyond science and technology

Nothing to report

5. Changes/Problems

5a. Changes in approach and reasons for change

No changes. We have received a 12-month no-cost extension to allow time to analyze the data following the completion of data collection.

5b. Actual or anticipated problems or delays and actions or plans to resolve them

No problems or delays anticipated.

5c. Changes that had a significant impact on expenditures

Subject compensation for travel and volunteer payments were reduced during the COVID pause (when a partial assessment was completed requiring less subject time). The cost savings has permitted us to bring those subjects into the office to complete the remainder of the testing in person (neurological exam and heart rate variability) for which they have been compensated. We will be able to complete the assessments and data analytic activities during the 12-month no-cost extension.

5d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

- Significant changes in use or care of human subjects None noted
- Significant changes in use or care of vertebrate animals NA
- Significant changes in use of biohazards and/or select agents NA

6. Products

- **Publications, conference papers, and presentations**
  Nothing to report
- **Website(s) or other Internet site(s)**
  Nothing to report
- **Technologies or techniques**
  Nothing to report
- **Inventions, patent applications, and/or licenses**
  Nothing to report
- **Other Products**
  Nothing to report

7. Participants & Other Collaborating Organizations

Name:	*Virginia A. Rauh, ScD*
Project Role:	*PI*

Researcher Identifier (e.g. ORCID ID):	*0000-0003-3164-9892*
Nearest person month worked:	*2.0*
Contribution to Project:	*Dr. Rauh has overseen all aspects of the project, including hiring training, protocol development, Human Subjects approvals, and met regularly with the research team.*
Funding Support:	*NA*

Name:	*Pullman, Seth*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	0000-0003-1604-7527
Nearest person month worked:	*1.0 cal months*
Contribution to Project:	*Dr. Pullman is supervising all tremor data collection and participating in preliminary data analytic activities*
Funding Support:	*NA*

Name:	*Kwei, Kimberly, MD*
Project Role:	*Movement disorders neurologist (junior faculty)*

Researcher Identifier (e.g. ORCID ID):	*0000-0002-0907-2807*
Nearest person month worked:	*1.0 cal months*
Contribution to Project:	*Dr. Kwei has clinically examined study participants, including administration of the MDS-UPDRS.*
Funding Support:	*NA*

Name:	*Elinol Lopez*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-6744-9924*
Nearest person month worked:	*9.0 cal months*
Contribution to Project:	*Ms. Lopez has made recruitment calls, consented and administered all questionnaires and cognitive tests.*
Funding Support:	*NA*

Name:	*Wanda Garcia*
Project Role:	*Project Coordinator*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-5559-2432*
Nearest person month worked:	*9.00 cal months*

Contribution to Project:	*Ms. Garcia has overseen all protocol activities, including the finalization of measures, IRB tasks, compensation of participants, scheduling, and data collection. She has organized regular staff meetings and ongoing internal reports.*
Funding Support:	*NA*

Name:	*Grace Liu*
Project Role:	*RA for Heart Rate Variability Analysis-Data Manager*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.0 cal months*
Contribution to Project:	*Responsibilities include collection and recording of data on each physiological signal. She is responsible for file storage on a shared, secured server; visual review of each type of data; and manually correcting invalid data points and/or annotating segments of unusable data via keyboard input.*
Funding Support:	*NA*

Name:	*Vincenzo Lauriola*
Project Role:	*Coordinator of autonomic data collection*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.0 cal months*
Contribution to Project:	*Responsibilities include oversight of autonomic data,*

	safety checks on abnormal signal, and interpretation of actiheart data analysis.
Funding Support:	*NA*

Name:	*David Merle*
Project Role:	*Database programmer*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1.0 cal months*
Contribution to Project:	*Merle is conducting data cleaning, entry and management*
Funding Support:	*NA*

- **Change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period**

Dr. Rauh has the following new grants since the last reporting period:

*Title: Ecological Study of the Comparative Health Effects of Housing Based Interventions

Major Goals: Building on the results of our planning project, and the work currently being undertaken to develop a data infrastructure system, the project's goal is to launch the first phase of a longitudinal study to implement and formally evaluate the co-benefits of greening and health-related effects of bundled intervention components for affordable housing residents across different sites.

*Status of Support: ACTIVE

Project Number: 2021-3068
Name of PD/PI: Rauh

*Source of Support: JPB Foundation

*Primary Place of Performance: Columbia University, New York, NY

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/01/2022-06/30/2025

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022-2023	1.0 cal months
2. 2023-2024	1.8 cal months
3. 2024-2025	1.8 cal months

*Title: Impact of climate change on neurological health of child tobacco workers: a new mechanistic paradigm to protect climate-vulnerable workers

Major Goals: To assess the impact of climate change on neurological health of child tobacco workers

*Status of Support: ACTIVE

Project Number: n/a

Name of PD/PI: Ziska and Rauh, MPI

*Source of Support: Research Initiatives in Science & Engineering (RISE) funding competition [Columbia University]

*Primary Place of Performance: Columbia University, New York, NY

Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/01/2022-05/31/2023

*Total Award Amount (including Indirect Costs):

*Person Months (Calendar/Academic/Summer) per budget period.

No measurable effort.

*Title: Brain and Behavioral Indicators of Risk for Parkinsonism among Adolescents with Early Pesticide Exposure [Supplement]

Major Goals: This proposal leverages the infrastructure and science of the parent study R01 ES030039 to apply our parkinsonian risk assessment methods (brain and behavioral) to better understand the pathogenesis of Alzheimer's Disease (AD) in a birth cohort of African American and Dominican American young adults—race/ethnic populations with the highest rates of AD, yet underrepresented in research studies.

*Status of Support: ACTIVE

Project Number: 5R01ES030039-04-S1 supplement

Name of PD/PI: Rauh, PI

*Source of Support: NIEHS

*Primary Place of Performance: Columbia University

Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/20/2022-12/31/2022

* Total Award Amount (including Indirect Costs):

* Person Months (Calendar/Academic/Summer) per budget period.

Year (2021)	Person Months (##.##)
1. Y1 2022	2.4 cal months

8. Special Reporting Requirements

- **QUAD CHARTS:**

9. Appendices